Organ protection in allograft recipients: anesthetic strategies to reduce postoperative morbidity and mortality

Hovaguimian, Frédérique ; Schläpfer, Martin ; Beck-Schimmer, Beatrice

Abstract: PURPOSE OF REVIEW Organ protection remains a primary objective in the anesthetic management of patients undergoing transplantation. An ongoing effort has been made to develop strategies to improve graft outcome and reduce postoperative morbidity and mortality, but trials have reported conflicting results. The aim of this review was to provide a comprehensive summary of the anesthetic management in transplant recipients and to identify current strategies for organ protection. RECENT FINDINGS Decreasing blood products requirements, intraoperative blood glucose control and adequate postoperative pain therapy may improve patient outcome. Vasopressors have been reported to reduce perioperative bleeding but might be associated with postoperative acute renal failure in liver transplantation. Early extubation may increase survival rates in recipients. These perioperative challenges, along with other protective strategies, have been addressed in 20 recently published studies: 10 randomized controlled trials, nine retrospective studies and one prospective study. SUMMARY This review identified several promising strategies ensuring organ protection and improving patient outcome after solid organ transplantation. However, as outcomes were difficult to compare, further evidence will be needed before drawing firm conclusions.

DOI: https://doi.org/10.1097/MOT.0000000000000062

Organ protection in allograft recipients: anesthetic strategies to reduce postoperative morbidity and mortality

Frédérique Hovaguimian[a], *Martin Schläpfer*[a,b], *and Beatrice Beck-Schimmer*[a,b]

Purpose of review
Organ protection remains a primary objective in the anesthetic management of patients undergoing transplantation. An ongoing effort has been made to develop strategies to improve graft outcome and reduce postoperative morbidity and mortality, but trials have reported conflicting results. The aim of this review was to provide a comprehensive summary of the anesthetic management in transplant recipients and to identify current strategies for organ protection.

Recent findings
Decreasing blood products requirements, intraoperative blood glucose control and adequate postoperative pain therapy may improve patient outcome. Vasopressors have been reported to reduce perioperative bleeding but might be associated with postoperative acute renal failure in liver transplantation. Early extubation may increase survival rates in recipients. These perioperative challenges, along with other protective strategies, have been addressed in 20 recently published studies: 10 randomized controlled trials, nine retrospective studies and one prospective study.

Summary
This review identified several promising strategies ensuring organ protection and improving patient outcome after solid organ transplantation. However, as outcomes were difficult to compare, further evidence will be needed before drawing firm conclusions.

Keywords
anesthesia, organ protection, postoperative complications, transplantation

INTRODUCTION

Over the past two decades, the perioperative management of patients undergoing solid organ transplantation sustained major developments, leading to a significant reduction in mortality and morbidity rates. In their 2011 statement, the Organ Procurement and Transplantation Network reported an overall increase in graft survival rates after kidney, heart, lung and liver transplantation [1▪–4▪]. Although 1-year survival after liver transplantation was only 33% in 1985, this proportion has been recently suggested to reach 85% for patients transplanted after 2004 [5]. Similar improvement has been described in 1-year survival rates following lung transplantation (70% in 1995 versus 81% in 2011) and, to a moderate extent, after kidney transplantation [6,7].

However, despite outcome improvement, most patients undergoing transplantation are still at high risk for postoperative complications: immediate death rate has been reported to reach 3% for liver transplantation, whereas primary graft failure remains the leading cause of mortality within 30 days following lung transplantation [5,7]. Organ shortage, extended waiting periods or advanced age often results in patients presenting for surgery with end-stage disease and marked co-morbidities [8]. The

[a]Institute of Anesthesiology, University Hospital Zurich and [b]Institute of Physiology and Zurich Center for Integrative Human Physiology, University of Zurich, Switzerland

Correspondence to Beatrice Beck-Schimmer, MD, Institute of Anesthesiology, University Hospital Zurich, University of Zurich, Raemistrasse 100, CH-8091 Zurich, Switzerland. Tel: +41 44 255 2696; fax: +41 44 255 4409; e-mail: beatrice.beckschimmer@uzh.ch

Curr Opin Organ Transplant 2014, 19:121–130
DOI:10.1097/MOT.0000000000000062

KEY POINTS

- Graft outcome may be predetermined by intraoperative events.
- Anesthetic strategies may ensure organ protection and improve patient outcome.
- Reducing blood products requirements, the use of vasopressors, early extubation, perioperative glucose control or adequate pain therapy may reduce postoperative complications.
- Further evidence will be needed, as trial designs, comparisons and endpoints differed widely among studies.

complexity of these cases usually requires multidisciplinary involvement at all levels, from the preoperative assessment until hospital discharge.

It has been suggested that some measures specifically related to the anesthetic management may offer organ protection and that several intraoperative factors could play a fundamental role in the development of postoperative complications [9–11]. The aim of this review was to provide a summary of recently published studies reporting on intraoperative strategies intended to reduce postoperative morbidity and mortality after solid organ transplantation.

METHODS

We performed a comprehensive search for relevant reports published in the Medline database between January 2012 and December 2013, using the key words 'anesthesia' and 'transplantation', without language restriction. We considered only fully published reports performed in adult patients (≥18 year old), undergoing any type of solid organ transplantation and that reported on any anesthetic strategy aiming at reducing postoperative morbidity and mortality. Anesthetic strategies were defined as any intervention occurring during the intraoperative phase, with the exception of specific surgical strategies (procurement, graft storage or surgical technique, for instance).

Data from animal, donor or pediatric studies were not considered. Reports in which patients underwent other procedures than solid organ transplantation (stem cells, islets, skin, face, extremities) were excluded. Data from studies without a comparison group (cross-sectional studies, surveys, observational cohort studies) were not considered. We also excluded trials realized in a different setting than intraoperative and/or considering factors occurring outside the intraoperative phase (for instance, preoperative patient optimization or postoperative strategies during the intensive care stay). Trials reporting on other outcomes than postoperative complications were not considered.

We considered reports with various levels of evidence [randomized controlled trials (RCTs), prospective studies, case–control studies] [12] but included only original articles. However, in an attempt to provide data of high quality, this article will focus primarily on RCT.

SYNTHESIS OF RESULTS

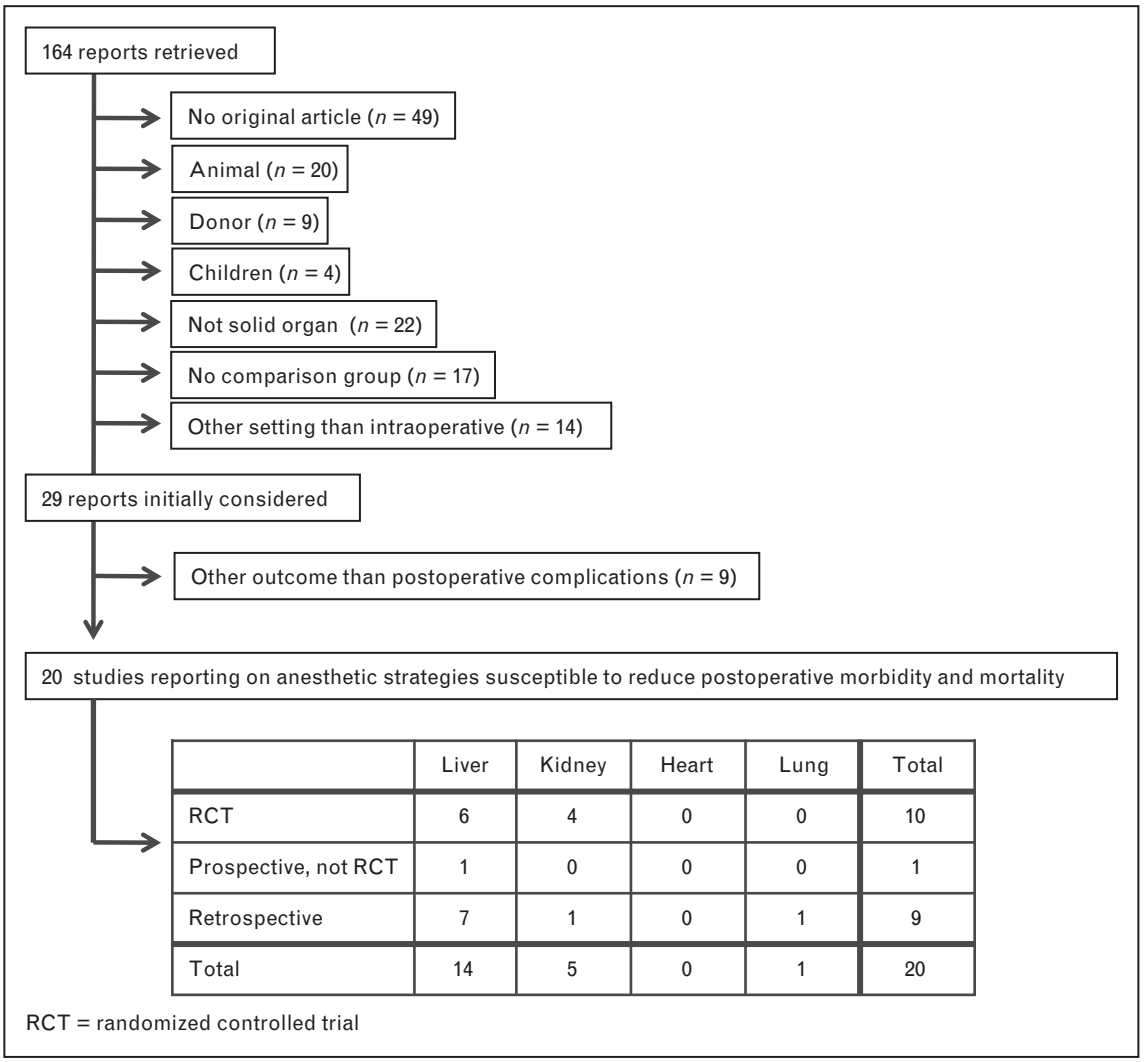
The last online search was performed December 14, 2013: 164 articles were initially considered (Fig. 1). Further examination led to the exclusion of nine studies describing other outcomes than postoperative complications [13–21].

Twenty studies reporting on anesthetic strategies aiming at reducing postoperative morbidity and mortality were eventually included (Table 1) [22–41]. We retrieved 14 studies reporting on postoperative complications in patients undergoing liver transplantation [22–24,28,29,31–33,35–37, 39–41], five studies conducted in kidney recipients [26,27,30,34,38] and one reporting on lung recipients [25].

BLEEDING DURING LIVER TRANSPLANTATION

An increasing number of studies have suggested that the administration of blood products in patients undergoing liver transplantation was associated with poor outcome [42–48], thus encouraging the development of new strategies to reduce blood products requirements. The intraoperative phase remains crucial, as surgical technique and anesthetic management play a determinant role in the prevention of bleeding.

Ongoing efforts have been made to identify predictors of perioperative bleeding. Patients undergoing liver transplantation have multiple reasons to suffer from major blood loss: preoperative coagulopathy (impaired factor synthesis, increased consumption or platelet disorders), major surgical trauma or intraoperative adverse events (technical difficulty, hypothermia, acidosis, hyperfibrinolysis) are all contributing factors to perioperative hemorrhage [49▪▪,50]. The necessity to coordinate both anesthetic and surgical endeavor during the operation has been underlined in a recent analysis, suggesting that patients with an anhepatic time of at least 60 min duration were at higher risk for perioperative bleeding and subsequent transfusion requirements [31].



	Liver	Kidney	Heart	Lung	Total
RCT	6	4	0	0	10
Prospective, not RCT	1	0	0	0	1
Retrospective	7	1	0	1	9
Total	14	5	0	1	20

RCT = randomized controlled trial

FIGURE 1. Study selection and detailed search results.

In a case–control study analyzing data from 522 patients undergoing liver transplantation, Wu *et al.* [40] identified factors associated with re-laparotomy for postoperative bleeding. Major blood loss and subsequent administration of blood products other than red blood cells (RBCs) [i.e. fresh frozen plasma (FFP), platelets (PLT) or cryoprecipitate] were associated with a higher rate of re-exploration for hemostasis. However, these results should be interpreted with caution, as many confounders intervene in retrospective studies: increased blood product requirements and subsequent re-exploration could be the result of inadequate primary hemostasis, rather than the consequence of blood product administration.

Similarly, Fayed *et al.* [24] investigated the occurrence of perioperative complications in 152 patients, who were subdivided in normal versus low preoperative platelet count (cutoff: 50×10^9/l). Interestingly, patients starting with a low baseline platelet count were not at higher risk regarding perioperative hemorrhage or blood product requirement, except for FFP. Data from each group were further analyzed according to the administration of PLT: patients who received PLT transfusions had higher complication rates (bleeding, duration of mechanical ventilation and ICU stay), regardless of their initial baseline platelet count. But here again, caution is required: because PLT transfusion was not prospectively assessed, these data might be the result of confounders that were not adequately controlled.

STRATEGIES TO REDUCE PERIOPERATIVE BLEEDING IN LIVER RECIPIENTS

Providing a rapid bedside coagulation assessment, thromboelastography (TEG) revolutionized the intraoperative management of patients undergoing major surgical procedures. The use of TEG-guided transfusion strategies has been suggested to reduce the administration of FFP and PLT [51,52], and TEG is nowadays integrated in most centers' guidelines.

Table 1. Characteristics of included studies

Reference	Surgery	Study design [not considered]	No. of patients analyzed	Comparison [not considered]		Endpoints
Bindi *et al.* [22]	Liver	RCT	63	Solvent/detergent plasma	FFP	Intra-OP: coagulation parameters; TEG; transfusion requirements; Post-OP: need for postoperative mechanical ventilation; need for dialysis; ICU LOS; mortality
Fayed *et al.* [23]	Liver	RCT	80	Terlipressin	Placebo	Intra-OP: hemodynamics; vasopressors requirements; blood loss; Post-OP: hepatic and renal arterial Doppler; liver tests; creatinine; urine output
Hong *et al.* [28]	Liver	RCT	41	Terlipressin	Placebo	Intra-OP: hemodynamics; blood loss; fluid/transfusion requirement; urine output Post-OP: peak creatinine level; time to extubation; ICU LOS; mortality; diverse complications.
Hong *et al.* [29]	Liver	RCT	76	Phenylephrine	Dopamine/ Dobutamine	Intra-OP: blood loss; fluids/transfusion requirements; urine output Post-OP: mortality; time to extubation; ICU LOS; diverse complications
Sahmeddini *et al.* [37]	Liver	RCT	79	Octreotide	Placebo	Intra-OP: hemodynamics; fluids/transfusion requirements; urine output Post-OP: creatinine; PGD; need for dialysis
Xia *et al.* [41]	Liver	RCT	40	Nicorandil	Placebo	Intra-OP: hemodynamics; blood loss; fluids/transfusion requirements; Post-OP: Mini-Mental State Examination; serum neuron-specific enolase; S100β protein
Fayed *et al.* [24]	Liver	1. Prospective 2. Retrospective	152	1. PC $\geq 50 \times 10^9$/l. 2. PLT transfusion	1. PC $< 50 \times 10^9$/l. 2. No PLT transfusion	Intra-OP: PLT count; coagulation parameters; blood loss; fluids/transfusion requirement; Post-OP: time to extubation; ICU LOS; thrombotic events; bleeding
Perilli *et al.* [35]	Liver	[1.Prospective] 2. Retrospective	38	[1. Esophageal Doppler]. 2. PGD	[1. Pulm. art. catheter]. 2. No PGD	Intra-OP: hemodynamics; blood loss; vasopressors requirements Post-OP: ICU LOS;
Kong *et al.* [31]	Liver	Retrospective	50	Anhepatic time $\geq$60 min	Anhepatic time $<$60 min	Peri-OP: coagulation parameters; blood loss; transfusion requirements
Krzanicki *et al.* [32]	Liver	Retrospective	124	1. TEG: Short R-time. 2. TEG: High G value.	1. TEG: Normal R-time. 2. TEG: Low G value.	Intra-OP: TEG values; coagulation parameters; transfusion requirements Post-OP: thrombotic events
Li *et al.* [33]	Liver	Retrospective	25	POCD	No POCD	Intra-OP: Beta-amyloid protein; CRP; blood transfusion Post-OP: MMSE; neuropsychological tests; graft function; time to extubation; ICU and hospital LOS; 1-year survival

Romano *et al.* [36]	Liver	Retrospective	92	AKI	No AKI	Intra-OP: hemodynamics; fluids/transfusion/terlipressin requirements; Post-OP: lactates, vasopressors requirements need for re-transplantation; mortality
Taner *et al.* [39]	Liver	Retrospective	870	PACU + Ward	ICU	Intra-OP: surgery time; transfusion requirements; Post-OP: graft survival; hospital LOS; diverse complications
Wu *et al.* [40]	Liver	Retrospective	522	Surgical re-exploration	No surgical re-exploration	Peri-OP: blood loss; fluids/transfusion requirements; urine output
Freir *et al.* [26]	Kidney	RCT	65	TAP block	Sham block	Post-OP: serum creatinine; blood urea; total morphine consumption; pain scores; PONV; sedation; respiratory depression
Hadimioglu *et al.* [27]	Kidney	RCT	46	EDA + GA	GA alone	Peri-OP: hemodynamics; glucose; insulin; inflammation markers; serum creatinine; hospital LOS
Kim *et al.* [30]	Kidney	RCT	60	Plasmalyte	Physiological saline	Intra-OP: acid-base status; fluids/transfusion requirements; blood loss; urine output; Post-OP: serum creatinine; serum chloride; urine output; primary graft failure; hospital LOS
Soltani *et al.* [38]	Kidney	RCT	44	TAP block	Sham block	Post-OP: pain scores; morphine consumption; PONV; complications (intoxications)
Parekh *et al.* [34]	Kidney	Retrospective	976	DGF	Immediate graft function	Several patient or allograft related factors; Peri-OP: blood glucose
Felten *et al.* [25]	Lung	Retrospective	128	PGD (grade III)	PGD (grades I and II)	Intra-OP: use of EDA; use of NO; use of CPB/ECMO; transfusion requirements; antifibrinolytic administration; need for vasopressors; urine output; Post-OP: time to extubation; lactate levels; PaO2/FiO2 ratio

AKI, acute kidney injury; CPB, cardiopulmonary bypass; DGF, delayed graft function; ECMO, extracorporeal membrane oxygenation; EDA, epidural anesthesia; FFP, fresh frozen plasma; GA, general anesthesia; Intra-OP, intraoperative; LOS, length of stay; NO, nitric oxide; PACU, postanesthesia care unit; PC, platelet count; Peri-OP, perioperative; PGD, primary graft disease; PLT, platelets; POCD, postoperative cognitive disorder; PONV, postoperative nausea and vomiting; Post-OP, postoperative; RCT, randomized controlled trial; TAP, transversus abdominis plane; TEG, thromboelastography.

TEG values may also be used to detect intraoperative hypercoagulability, which has been associated with an increased risk of thromboembolic complications [53,54]. Krzanicki *et al.* [32] investigated the association of hypercoagulation with perioperative thrombotic events in 124 liver recipients but were, however, unable to confirm findings described previously.

The administration of FFP has been the center of debate for many years and still remains a controversial issue. In a recently published Cochrane review, several methods to decrease blood loss during liver transplantation were analyzed [55]. Most retrieved studies were at high risk of bias, underlining the need for well designed randomized trials to eventually reach consensus. Bindi *et al.* [22] compared solvent/detergent-treated plasma to FFP in 63 patients undergoing orthotopic liver transplantation (OLT). Solvent detergent-treated plasma has been developed by pharmaceutical industry to reduce the transmission of transfusion-related viral infections. Because of the filtration and inactivation process, solvent/detergent-treated plasma has been suggested to have a lower coagulation factors and inhibitors content compared with FFP [49▪▪]. In the Bindi trial, there was no difference in fluid requirements, RBC/PLT transfusion, need for postoperative mechanical ventilation or renal replacement therapy (RRT), length of ICU stay and survival at hospital discharge. Additional trials will be needed to confirm these results.

Vasoconstrictors play a key role in hemodynamic management during liver transplantation. Their specific action on splanchnic circulation might decrease blood flow to the liver, thus reducing bleeding and blood products requirements. Three RCT compared the administration of vasopressors during liver transplantation [23,28,29]. In one trial [29], 76 patients received either phenylephrine or dopamine/dobutamine. The estimated blood loss, RBC and FFP transfusion were significantly lower in the phenylephrine group. In a trial comparing terlipressin with noradrenaline in 80 patients [23], terlipressin was found to reduce significantly perioperative bleeding. However, a smaller trial failed to confirm these findings [28].

As no clear superiority has been determined yet, most authors recommend the use of phenylephrine and norepinephrine for hemodynamic management in liver transplantation [56].

ACUTE RENAL FAILURE AFTER LIVER TRANSPLANTATION

Acute kidney injury (AKI) is a crucial issue for patients undergoing OLT and has been reported to occur in approximately 60% of patients postoperatively [57]. In this analysis, RRT was required in 8.6% of cases and mortality rates were significantly higher in AKI-patients compared with non-AKI patients (15.5 and 25.9% compared with 0 and 3.9%, respectively) [57].

Our search retrieved five articles: one case–control analysis evaluated the association between postoperative AKI and perioperative factors [36], whereas four were RCTs comparing different vasoactive drugs. AKI was the primary outcome in two [23,37], whereas the other trials reported a variety of data, including markers of the renal function [28,29].

In the analysis of Romano *et al.* [36], postoperative AKI was present in 56.6% of patients. Factors associated with AKI were: Model for End-Stage Liver Disease (MELD) score, preoperative bilirubin and INR, the use of terlipressin during surgery, blood products administration and a higher dose of noradrenalin at ICU admission. Karapanagiotou and coll. [58] reported a statistically significant association between AKI and the use of vasoactive drugs.

Cirrhotic patients undergoing OLT are at risk to develop hepatorenal syndrome: portal hypertension leads to splanchnic vasodilatation with subsequent intrarenal vasoconstriction and poor renal perfusion [59]. Vasoactive drugs have been suggested to increase the splanchnic vascular tone, restore an adequate renal perfusion and be effective in 40–50% of patients with hepatorenal syndrome [60]. Their use in the transplantation setting is, however, still controversial. Sahmeddini and coll. [37] investigated the protective effect of octreotide on renal function in 89 patients: the octreotide group had a significantly higher urine output, but there was no difference in the postoperative serum creatinine levels or need for RRT. Data regarding terlipressin remain inconclusive: in retrospective studies, the use of terlipressin was associated with AKI [36], but RCT were not able to confirm this detrimental effect [23,28].

Additional evidence will be needed to establish recommendations for the management of AKI in liver recipients.

PRIMARY GRAFT FAILURE, COGNITIVE DYSFUNCTION AND OTHER COMPLICATIONS IN LIVER RECIPIENTS

Primary graft failure remains an important cause of mortality and one of the leading indications for retransplantation in liver recipients [5]. A variety of intraoperative strategies with the aim to improve graft outcome has been investigated. Most retrieved studies reported on surrogate markers of liver

function but few were focusing specifically on primary graft dysfunction (PGD). These findings are summarized in Table 2.

Neurological complications following major surgery are frequent, and their incidence has been reported to reach 29.4% in patients undergoing OLT [61]. A case-control study reported a significant association between postoperative cognitive dysfunction, MELD scores and intraoperative blood transfusion, but the small patient population and the study design dampened these results [33]. Nicorandil, a vasodilator with nitrate properties, has been reported to have cerebral protective effects in neuronal injury models [62]. Similar findings were reported by Xia *et al.* [41] in a trial comparing nicorandil with physiological saline in 40 patients undergoing liver transplantation: Mini-Mental-State examination scores were significantly higher in the nicorandil group.

The impact of early extubation after liver transplantation remains still under debate. This strategy has been suggested to improve graft outcome, decrease pulmonary complications and reduce the economical burden related to ICU stay [40]. In a large retrospective analysis, 513 liver recipients were extubated immediately after surgical procedure and subsequently transferred to the ward without ICU stay (fast-track strategy) [39]. Although these patients had significantly shorter hospital stays and increased survival rates, it remains unclear if this benefit resulted from the fast-track strategy *per se* or if it was the consequence of patient selection. One may argue that the fast-tracked population was significantly healthier and had less intraoperative complications.

DELAYED GRAFT FUNCTION AFTER KIDNEY TRANSPLANTATION

Delayed graft function (DGF), defined as the need for RRT within 7 days of transplantation, vary from 27.3% in deceased donor kidney recipients [63] to more than 60% with the use of expanded criteria donor allografts [64]. In a retrospective analysis of 976 kidney recipients, DGF occurred in 21.6% of patients and was more common in diabetic patients with postoperative glucose greater than 160 mg/dl [34]. The authors identified several perioperative risk factors associated with DGF; interestingly, glucose level was the only intraoperative modifiable factor associated with DGF.

PERIOPERATIVE FLUID MANAGEMENT IN KIDNEY RECIPIENTS

Ensuring an adequate diuresis after graft anastomosis is a major concern as low urine output has been associated with lower graft survival rates [65]. Even though a form of consensus on the risk of AKI after hydroxyethyl starches administration has probably been reached [66], it remains unclear which crystalloid infusion should be used during kidney transplantation. Kim *et al.* [30] compared physiological saline with the administration of Plasmalyte, a crystalloid solution comparable with human plasma in terms of osmolality, pH and electrolytes content. Although pH values were lower in the physiological saline group, postoperative outcomes did not differ between groups (serum creatinine, urine output, need for RRT). These results are consistent with earlier findings on the same issue [67].

Table 2. Primary graft failure: endpoints and results

References	Study design	No. of patients analyzed	Comparison		Endpoints	Results
Fayed *et al.* [23]	RCT	80	Terlipressin	Placebo	Hepatic Doppler ultrasonography	Hepatic arterial resistive indices and portal venous blood flow significantly decreased in terlipressin group
					Liver tests, lactate	No difference between groups
Hong *et al.* [28]	RCT	41	Terlipressin	Placebo	Graft rejection	No difference between groups
					Hepatic artery thrombosis	No difference between groups
Hong *et al.* [29]	RCT	76	Phenylephrine	Dopamine/ dobutamine	INR, bilirubin	No difference between groups
					Graft rejection, early graft dysfunction	No difference between groups
Sahmeddini *et al.* [37]	RCT	79	Octreotide	Placebo	Primary nonfunction	No difference between groups

INR, international normalized ratio (prothrombin time); RCT, randomized controlled trial.

PAIN CONTROL AFTER KIDNEY TRANSPLANTATION

The benefits of regional anesthesia in kidney transplantation have been widely debated in the past 10 years. Epidural anesthesia, combined with general anesthesia or in combination with spinal anesthesia, has been suggested to provide better postoperative pain control [68]. Epidural anesthesia has been reported to reduce respiratory complications in patients undergoing major abdominal surgery [69], but this effect has not been established in the transplantation setting yet.

Epidural anesthesia combined with general anesthesia was compared with general anesthesia alone in 46 kidney recipients [27]. Significant differences were reported for serum glucose, insulin, inflammation markers (tumor necrosis factor-α, TNF-α and interleukin-6, IL-6) and hospital length of stay, suggesting a global protective effect with epidural anesthesia.

Two RCT comparing the efficacy of transversus abdominis plane (TAP) block for postoperative pain relief reported contradictory results [26,38]. Although TAP block has been demonstrated to provide effective analgesia in various surgical settings [70–72], its efficacy remains to be determined in patients undergoing kidney transplantation.

PRIMARY GRAFT DYSFUNCTION IN LUNG RECIPIENTS

Felten *et al.* [25] reported on a variety of intraoperative factors associated with the occurrence of PGD. In their analysis, 122 recipients were divided into three groups, according to their grade of PGD (grade I: $PaO_2/FiO_2 > 300$ mmHg; grade II: $PaO_2/FiO_2 = 200–300$ mmHg; grade III: $PaO_2/FiO_2 <$ 200 mmHg). Intraoperative RBC administration was associated with a significant higher risk to develop Grade III PGD. In a similar study [73▪▪], intraoperative transfusion of RBC and FFP was associated with a significant increase in mortality after lung transplantation in 134 patients.

FUTURE PERSPECTIVES

To date, there is still no consensus on the best drug to achieve anesthesia maintenance during solid organ transplantation [9,56]. Volatile anesthetics have been suggested to provide protection against ischemia–reperfusion injury in a variety of surgical settings [74–76]. Their effect in the transplantation setting is the primary focus of several trials that are still in progress (NCT00913276; NCT01248871; NCT01936545; NCT00337051; NCT01870011; NCT02009280; NCT01132157 in: clinicaltrials.gov).

The use of nitric oxide (NO) donor agents has been suggested to reduce ischemia–reperfusion injury in liver and lung recipients [77], but few studies have reported high-quality data. The administration of NO is being currently investigated in three trials (NCT00582010; NCT01172691; NCT00948194 in: clinicaltrials.gov).

CONCLUSION

Considerable efforts have been made to identify intraoperative factors associated with postoperative complications. Our search retrieved several promising strategies to ensure organ protection and improve patient outcome such as decreasing blood products requirements, adequate blood glucose control or the use of regional anesthesia if possible. However, results were difficult to compare, as study designs, comparisons and endpoints differed widely among reports. The debate on intraoperative organ protection seems, therefore, to have just started and further evidence will be needed before drawing firm conclusions.

Acknowledgements

None.

Conflicts of interest

This study received financial support from institutional funds only. The funding source had no role in: the extraction, management, analysis, or interpretation of the data; in the preparation, review, or approval of the manuscript.

Financial disclosure: Support was provided solely from institutional sources.

The authors have no conflicts of interest to declare.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Colvin-Adams M, Smith JM, Heubner BM, *et al.* OPTN/SRTR 2011 Annual ▪ Data Report: heart. Am J Transplant 2013; 13 (Suppl 1):119–148.
Informative report of the US Organ Procurement and Transplantation Network. Comprehensive summary of US data providing detailed background informations.
2. Kim WR, Stock PG, Smith JM, *et al.* OPTN/SRTR 2011 Annual Data Report: ▪ liver. Am J Transplant 2013; 13 (Suppl 1):73–102.
Informative report of the US Organ Procurement and Transplantation Network. Comprehensive summary of US data providing detailed background informations.
3. Matas AJ, Smith JM, Skeans MA, *et al.* OPTN/SRTR 2011 Annual Data ▪ Report: kidney. Am J Transplant 2013; 13 (Suppl 1):11–46.
Informative report of the US Organ Procurement and Transplantation Network. Comprehensive summary of US data providing detailed background informations.
4. Valapour M, Paulson K, Smith JM, *et al.* OPTN/SRTR 2011 Annual Data ▪ Report: lung. Am J Transplant 2013; 13 (Suppl 1):149–177.
Informative report of the US Organ Procurement and Transplantation Network. Comprehensive summary of US data providing detailed background information.
5. Adam R, Karam V, Delvart V, *et al.* Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). J Hepatol 2012; 57:675–688.

6. Kramer A, Stel V, Zoccali C, *et al.* An update on renal replacement therapy in Europe: ERA-EDTA Registry data from 1997 to 2006. Nephrol Dial Transplant 2009; 24:3557–3566.
7. Yusen RD, Christie JD, Edwards LB, *et al.* The Registry of the International Society for Heart and Lung Transplantation: thirtieth adult lung and heart-lung transplant report – 2013; focus theme: age. J Heart Lung Transplant 2013; 32:965–978.
8. Lentine KL, Costa SP, Weir MR, *et al.* Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the American Heart Association and the American College of Cardiology Foundation: endorsed by the American Society of Transplant Surgeons, American Society of Transplantation, and National Kidney Foundation. Circulation 2012; 126:617–663.
9. Hall TH, Dhir A. Anesthesia for liver transplantation. Semin Cardiothorac Vasc Anesth 2013; 17:180–194.
10. Ricaurte L, Vargas J, Lozano E, Diaz L. Anesthesia and kidney transplantation. Transplant Proc 2013; 45:1386–1391.
11. Valentine E, Gregorits M, Gutsche JT, *et al.* Clinical update in liver transplantation. J Cardiothorac Vasc Anesth 2013; 27:809–815.
12. Guyatt GH, Haynes RB, Jaeschke RZ, *et al.* Users' Guides to the Medical Literature: XXV. Evidence-based medicine: principles for applying the Users' Guides to patient care. Evidence-Based Medicine Working Group. JAMA 2000; 284:1290–1296.
13. Han SB, Gwak MS, Choi SJ, *et al.* Effect of active airway warming on body core temperature during adult liver transplantation. Transplant Proc 2013; 45:251–254.
14. Hasanin AS, Mahmoud FM, Yassen KA. Entropy-guided end-tidal desflurane concentration during living donor liver transplantation. Saudi J Anaesth 2013; 7:399–403.
15. Huh IY, Kim YK, Shin WJ, *et al.* Increased B-type natriuretic peptide during liver transplantation: relationship to invasively measured hemodynamic parameters. Transplant Proc 2012; 44:1318–1322.
16. Okada T, Kawahito S, Mita N, *et al.* Usefulness of continuous blood glucose monitoring and control for patients undergoing liver transplantation. J Med Invest 2013; 60:205–212.
17. Rosendal C, Almamat Uulu K, De Simone R, *et al.* Right ventricular function during orthotopic liver transplantation: three-dimensional transesophageal echocardiography and thermodilution. Ann Transplant 2012; 17:21–30.
18. Sahmeddini MA, Eghbal MH, Khosravi MB, *et al.* Electro-acupuncture stimulation at acupoints reduced the severity of hypotension during anesthesia in patients undergoing liver transplantation. J Acupunct Meridian Stud 2012; 5:11–14.
19. Su BC, Tsai YF, Chen CY, *et al.* Cardiac output derived from arterial pressure waveform analysis in patients undergoing liver transplantation: validity of a third-generation device. Transplant Proc 2012; 44:424–428.
20. Su BC, Tsai YF, Cheng CW, *et al.* Stroke volume variation derived by arterial pulse contour analysis is a good indicator for preload estimation during liver transplantation. Transplant Proc 2012; 44:429–432.
21. Tsai YF, Lin CC, Lee WC, Yu HP. Propofol attenuates ischemic reperfusion-induced formation of lipid peroxides in liver transplant recipients. Transplant Proc 2012; 44:376–379.
22. Bindi ML, Miccoli M, Marietta M, *et al.* Solvent detergent vs. fresh frozen plasma in cirrhotic patients undergoing liver transplant surgery: a prospective randomized control study. Vox Sang 2013; 105:137–143.
23. Fayed N, Refaat EK, Yassein TE, Alwaraqy M. Effect of perioperative terlipressin infusion on systemic, hepatic, and renal hemodynamics during living donor liver transplantation. J Crit Care 2013; 28:775–782.
24. Fayed NA, Roshdy AA, Khalil MK, Marwan IK. Therapeutic rather than prophylactic platelet transfusion policy for severe thrombocytopenia during liver transplantation. Platelets 2013. [Epub ahead of print]
25. Felten ML, Sinaceur M, Treilhaud M, *et al.* Factors associated with early graft dysfunction in cystic fibrosis patients receiving primary bilateral lung transplantation. Eur J Cardiothorac Surg 2012; 41:686–690.
26. Freir NM, Murphy C, Mugawar M, *et al.* Transversus abdominis plane block for analgesia in renal transplantation: a randomized controlled trial. Anesth Analg 2012; 115:953–957.
27. Hadimioglu N, Ulugol H, Akbas H, *et al.* Combination of epidural anesthesia and general anesthesia attenuates stress response to renal transplantation surgery. Transplant Proc 2012; 44:2949–2954.
28. Hong SH, Lee JM, Choi JH, *et al.* Perioperative assessment of terlipressin infusion during living donor liver transplantation. J Int Med Res 2012; 40:225–236.
29. Hong SH, Park CS, Jung HS, *et al.* A comparison of intra-operative blood loss and acid-base balance between vasopressor and inotrope strategy during living donor liver transplantation: a randomised, controlled study. Anaesthesia 2012; 67:1091–1100.
30. Kim SY, Huh KH, Lee JR, *et al.* Comparison of the effects of normal saline versus Plasmalyte on acid-base balance during living donor kidney transplantation using the Stewart and base excess methods. Transplant Proc 2013; 45:2191–2196.
31. Kong HY, Huang SQ, Zhu SM, Wen XH. Role of anhepatic time in endothelial-related coagulation in liver transplantation. Minerva Anestesiol 2013; 79:391–397.
32. Krzanicki D, Sugavanam A, Mallett S. Intraoperative hypercoagulability during liver transplantation as demonstrated by thromboelastography. Liver Transpl 2013; 19:852–861.
33. Li X, Wen DX, Zhao YH, *et al.* Increase of beta-amyloid and C-reactive protein in liver transplant recipients with postoperative cognitive dysfunction. Hepatobiliary Pancreat Dis Int 2013; 12:370–376.
34. Parekh J, Roll GR, Feng S, *et al.* Peri-operative hyperglycemia is associated with delayed graft function in deceased donor renal transplantation. Clin Transplant 2013; 27:E424–E430.
35. Perilli V, Aceto P, Modesti C, *et al.* Low values of left ventricular ejection time in the postanhepatic phase may be associated with occurrence of primary graft dysfunction after orthotopic liver transplantation: results of a single-centre case-control study. Eur Rev Med Pharmacol Sci 2012; 16:1433–1440.
36. Romano TG, Schmidtbauer I, Silva FM, *et al.* Role of MELD score and serum creatinine as prognostic tools for the development of acute kidney injury after liver transplantation. PLoS One 2013; 8:e64089.
37. Sahmeddini MA, Amini A, Naderi N. The effect of octreotide on urine output during orthotopic liver transplantation and early postoperative renal function; a randomized, double-blind, placebo-controlled trial. Hepat Mon 2013; 13:e12787.
38. Soltani Mohammadi S, Dabir A, Shoeibi G. Efficacy of transversus abdominis plane block for acute postoperative pain relief in kidney recipients: a double-blinded clinical trial. Pain Med 2013; 11:1–5.
39. Taner CB, Willingham DL, Bulatao IG, *et al.* Is a mandatory intensive care unit stay needed after liver transplantation? Feasibility of fast-tracking to the surgical ward after liver transplantation. Liver Transpl 2012; 18:361–369.
40. Wu SC, Chen CL, Wang CH, *et al.* Predictive factors associated with re-exploration for hemostasis in living donor liver transplantation. Ann Transplant 2012; 17:64–71.
41. Xia YF, Wang ZP, Zhou YC, *et al.* Cerebral protective effect of nicorandil premedication on patients undergoing liver transplantation. Hepatobiliary Pancreat Dis Int 2012; 11:132–136.
42. Boin IF, Leonardi MI, Luzo AC, *et al.* Intraoperative massive transfusion decreases survival after liver transplantation. Transplant Proc 2008; 40:789–791.
43. Boyd SD, Stenard F, Lee DK, *et al.* Alloimmunization to red blood cell antigens affects clinical outcomes in liver transplant patients. Liver Transpl 2007; 13:1654–1661.
44. Cacciarelli TV, Keeffe EB, Moore DH, *et al.* Effect of intraoperative blood transfusion on patient outcome in hepatic transplantation. Arch Surg 1999; 134:25–29.
45. Hendriks HG, van der Meer J, de Wolf JT, *et al.* Intraoperative blood transfusion requirement is the main determinant of early surgical re-intervention after orthotopic liver transplantation. Transpl Int 2005; 17:673–679.
46. Massicotte L, Sassine MP, Lenis S, *et al.* Survival rate changes with transfusion of blood products during liver transplantation. Can J Anaesth 2005; 52:148–155.
47. Nardo B, Bertelli R, Montalti R, *et al.* Red blood cell transfusion in liver transplantation: a case-control study. Transplant Proc 2005; 37:4389–4392.
48. Ramos E, Dalmau A, Sabate A, *et al.* Intraoperative red blood cell transfusion in liver transplantation: influence on patient outcome, prediction of requirements, and measures to reduce them. Liver Transpl 2003; 9:1320–1327.
49. ■■ Feltracco P, Brezzi M, Barbieri S, *et al.* Blood loss, predictors of bleeding, transfusion practice and strategies of blood cell salvaging during liver transplantation. World J Hepatol 2013; 5:1–15.

Excellent review providing current strategies to manage perioperative bleeding in liver recipients.

50. Massicotte L, Denault AY, Beaulieu D, *et al.* Transfusion rate for 500 consecutive liver transplantations: experience of one liver transplantation center. Transplantation 2012; 93:1276–1281.
51. Wang SC, Shieh JF, Chang KY, *et al.* Thromboelastography-guided transfusion decreases intraoperative blood transfusion during orthotopic liver transplantation: randomized clinical trial. Transplant Proc 2010; 42:2590–2593.
52. Wikkelsoe AJ, Afshari A, Wetterslev J, *et al.* Monitoring patients at risk of massive transfusion with Thrombelastography or Thromboelastometry: a systematic review. Acta Anaesthesiol Scand 2011; 55:1174–1189.
53. Kashuk JL, Moore EE, Sabel A, *et al.* Rapid thrombelastography (r-TEG) identifies hypercoagulability and predicts thromboembolic events in surgical patients. Surgery 2009; 146:764–772.
54. McCrath DJ, Cerboni E, Frumento RJ, *et al.* Thromboelastography maximum amplitude predicts postoperative thrombotic complications including myocardial infarction. Anesth Analg 2005; 100:1576–1583.
55. Gurusamy KS, Pissanou T, Pikhart H, *et al.* Methods to decrease blood loss and transfusion requirements for liver transplantation. Cochrane Database Syst Rev 2011; 7:CD009052.
56. Spiro MD, Eilers H. Intraoperative care of the transplant patient. Anesthesiol Clin 2013; 31:705–721.
57. Zhu M, Li Y, Xia Q, *et al.* Strong impact of acute kidney injury on survival after liver transplantation. Transplant Proc 2010; 42:3634–3638.
58. Karapanagiotou A, Kydona C, Dimitriadis C, *et al.* Acute kidney injury after orthotopic liver transplantation. Transplant Proc 2012; 44:2727–2729.
59. Planinsic RM, Lebowitz JJ. Renal failure in end-stage liver disease and liver transplantation. Int Anesthesiol Clin 2006; 44:35–49.

60. Gines P, Schrier RW. Renal failure in cirrhosis. N Engl J Med 2009; 361:1279–1290.

61. Colombari RC, de Ataide EC, Udo EY, *et al.* Neurological complications prevalence and long-term survival after liver transplantation. Transplant Proc 2013; 45:1126–1129.

62. Teshima Y, Akao M, Baumgartner WA, Marban E. Nicorandil prevents oxidative stress-induced apoptosis in neurons by activating mitochondrial ATP-sensitive potassium channels. Brain Res 2003; 990:45–50.

63. Ghods AJ, Savaj S, Abbasi M, *et al.* The incidence and risk factors of delayed graft function in 689 consecutive living unrelated donor renal transplantation. Transplant Proc 2007; 39:846–847.

64. Chavalitdhamrong D, Gill J, Takemoto S, *et al.* Patient and graft outcomes from deceased kidney donors age 70 years and older: an analysis of the Organ Procurement Transplant Network/United Network of Organ Sharing database. Transplantation 2008; 85:1573–1579.

65. Dawidson I, Ar'Rajab A, Dickerman R, *et al.* Perioperative albumin and verapamil improve early outcome after cadaver renal transplantation. Transplant Proc 1994; 26:3100–3101.

66. Mutter TC, Ruth CA, Dart AB. Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. Cochrane Database Syst Rev 2013; 7:CD007594.

67. Hadimioglu N, Saadawy I, Saglam T, *et al.* The effect of different crystalloid solutions on acid-base balance and early kidney function after kidney transplantation. Anesth Analg 2008; 107:264–269.

68. Dauri M, Costa F, Servetti S, *et al.* Combined general and epidural anesthesia with ropivacaine for renal transplantation. Minerva Anestesiol 2003; 69:873–884.

69. Popping DM, Elia N, Marret E, *et al.* Protective effects of epidural analgesia on pulmonary complications after abdominal and thoracic surgery: a meta-analysis. Arch Surg 2008; 143:990–999.

70. Abdallah FW, Halpern SH, Margarido CB. Transversus abdominis plane block for postoperative analgesia after Caesarean delivery performed under spinal anaesthesia? A systematic review and meta-analysis. Br J Anaesth 2012; 109:679–687.

71. Abdallah FW, Laffey JG, Halpern SH, Brull R. Duration of analgesic effectiveness after the posterior and lateral transversus abdominis plane block techniques for transverse lower abdominal incisions: a meta-analysis. Br J Anaesth 2013; 111:721–735.

72. Johns N, O'Neill S, Ventham NT, *et al.* Clinical effectiveness of transversus abdominis plane (TAP) block in abdominal surgery: a systematic review and meta-analysis. Colorectal Dis 2012; 14:e635–e642.

73. ■■ Weber D, Cottini SR, Locher P, *et al.* Association of intraoperative transfusion of blood products with mortality in lung transplant recipients. Perioper Med 2013; 2.

Retrospective analysis in lung recipients pointing out possible detrimental effects of blood products on patient outcome.

74. Beck-Schimmer B, Breitenstein S, Bonvini JM, *et al.* Protection of pharmacological postconditioning in liver surgery: results of a prospective randomized controlled trial. Ann Surg 2012; 256:837–844.

75. Schifilliti D, Grasso G, Conti A, Fodale V. Anaesthetic-related neuroprotection: intravenous or inhalational agents? CNS Drugs 2010; 24:893–907.

76. Steurer MP, Steurer MA, Baulig W, *et al.* Late pharmacologic conditioning with volatile anesthetics after cardiac surgery. Crit Care 2012; 16:R191.

77. Roberts BW, Mitchell J, Kilgannon JH, *et al.* Nitric oxide donor agents for the treatment of ischemia/reperfusion injury in human subjects: a systematic review. Shock 2013; 39:229–239.